

What is claimed is:

1. A mutant of a protein, the protein causing a disease after having performed
5 a conformational transition, the disease comprising:
 - a) neurodegenerative diseases of the group comprising Transmissible Spongiform Encephalopathy (TSE), Alzheimers disease, Multiple Sclerosis, and Parkinsons disease; and/or other
 - b) conformational diseases of the group comprising Primary systematic
10 amyloidosis, Type II diabetes, and Atrial amyloidosis;wherein the mutant protein or a variant of which comprises at least one additional engineered disulfide bond which inhibits a conformational transition of such proteins in human and animals.
- 15 2. The protein of claim 1,
wherein the at least one additional disulfide bond is engineered at a position similar to a disulfide bond in a structurally related non-pathogenic protein.
3. The protein of claim 1,
20 wherein the protein is a prion protein, the at least one engineered additional disulfide bond being situated in the globular domain.
4. The prion protein of claim 3,
wherein the at least one engineered additional disulfide bond is situated in a
25 position similar as in the doppel protein (Dpl).
5. The prion protein of claim 3,
wherein the protein comprises a 'factor X' binding epitope and the at least
one engineered additional disulfide bond is situated within this 'factor X'
30 binding epitope.

6. The prion protein of claim 3,
wherein the at least one engineered additional disulfide bond is introduced
between a first segment comprising the amino acid residues 165-175 and a
second segment comprising the C-terminal amino acid residues 215-230 in
a human prion protein or between structurally corresponding amino acid
segments in other species.
7. The prion protein of claim 6,
wherein the at least one engineered additional disulfide bond is linking
amino acid residues M166C and E221C or amino acid residues M166C and
Y225C.
8. A nucleic acid sequence coding for a mutant protein, the protein causing a
disease after having performed a conformational transition, the disease
comprising:
- a) neurodegenerative diseases of the group comprising Transmissible
Spongiform Encephalopathy (TSE), Alzheimers disease, Multiple
Sclerosis, and Parkinsons disease; and/or other
 - b) conformational diseases of the group comprising Primary systematic
amyloidosis, Type II diabetes, and Atrial amyloidosis;
- wherein the nucleic acid sequence is coding for the mutant protein or a
variant of which that comprises at least one additional engineered disulfide
bond which inhibits a conformational transition of such proteins in human
and animals.
9. Plasmid constructs, vectors, transformed cells, transgenic animals including
cattle, sheep, cat, elk, and deer, and recombinant proteins, comprising
and/or being encoded by a nucleic acid sequence according to claim 8.

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10. Use of a mutant of a protein, the protein causing a disease after having performed a conformational transition, the disease comprising:

a) neurodegenerative diseases of the group comprising Transmissible Spongiform Encephalopathy (TSE), Alzheimers disease, Multiple Sclerosis, and Parkinsons disease; and/or other

b) conformational diseases of the group comprising Primary systematic amyloidosis, Type II diabetes, and Atrial amyloidosis;

the mutant protein or a variant of which comprising at least one additional engineered disulfide bond which inhibits a conformational transition of such proteins in human and/or animals, wherein the mutant protein is used for therapeutic treatment of conformational diseases.

11. Use of a mutant of a protein, the protein causing a disease after having performed a conformational transition, the disease comprising:

a) neurodegenerative diseases of the group comprising Transmissible Spongiform Encephalopathy (TSE), Alzheimers disease, Multiple Sclerosis, and Parkinsons disease; and/or other

b) conformational diseases of the group comprising Primary systematic amyloidosis, Type II diabetes, and Atrial amyloidosis;

the mutant protein or a variant of which comprising at least one additional engineered disulfide bond which inhibits a conformational transition of such proteins in human and/or animals, wherein the mutant protein is used for the manufacturing of a medicament for the therapeutic treatment of conformational diseases.

12. The use according to claim 10 or 11,

wherein the engineered additional disulfide bond(s) prevent(s) a conformational transition of mutant PrP^C into PrP^{Sc} and thus suppress(es) a conformational transition of PrP^C into PrP^{Sc} in co-existing wild-type proteins by dominant negative inhibition.

13. The use according to claim 10 or 11,
wherein the conformational transition of wild type PrP^C into PrP^{Sc} oligomers is
suppressed by binding of mutant PrP^C to wild-type PrP^C.

5 14. The use according to claim 10 or 11,
wherein the conformational transition of wild type PrP^{Sc} oligomers into PrP^{Sc}
amyloid fibrils is suppressed by binding of mutant PrP^C to wild-type PrP^{Sc} oli-
gomers.

10 15. The use according to claim 10 or 11,
wherein the conformational transition of wild type PrP^C into PrP^C/PrP^{Sc} het-
erodimers is suppressed by binding of mutant PrP^C to wild-type PrP^{Sc}.

15 16. The use according to claim 10 or 11,
wherein the elongation of amyloid fibrils or the dissociation of amyloid fibrils
into PrP^{Sc} oligomers is suppressed by binding of mutant PrP^C to wild-type
PrP^{Sc} amyloid fibrils.

20 17. The use according to claim 8, 9, 10, or 11,
wherein *in vivo* generation of disulfide mutants of prion proteins or variants
thereof is carried out in order to enable an intended therapy of
Transmissible Spongiform Encephalopathy (TSE) in human, e.g. by somatic
gene therapy with lentiviral vector, where TSE includes spontaneous, inher-
25 ited, iatrogenic and variant forms of Creutzfeldt-Jakob disease (CJD), fatal
familial insomnia (FFI), and Gerstmann-Sträussler-Scheinker syndrome
(GSS).

18. The use according to claim 10 or 11,
wherein the recombinant production of disulfide mutants of prion proteins or
variants thereof is carried out in order to enable an intended therapy of TSE
in human, e.g. by direct application of the recombinant protein, where TSE
5 includes spontaneous, inherited, iatrogenic and variant forms of CJD, FFI,
and GSS.
19. The use according to claim 8, 9, 10, or 11,
wherein *in vivo* generation of disulfide mutants of prion proteins or variants
10 thereof is carried out in order to enable an intended therapy of TSE in ani-
mals, e.g. by somatic gene therapy with lentiviral vector, where TSE in-
cludes bovine spongiform encephalopathy (BSE), scrapie in sheep, feline
spongiform encephalopathy (FSE), and chronic wasting disease (CWD) in elk
and deer.
20. The use according to claim 10 or 11,
wherein recombinant production of disulfide mutants of prion proteins or
variants thereof is carried out in order to enable an intended therapy of TSE
in animals, e.g. by direct application of the recombinant protein, where TSE
20 includes BSE, scrapie, FSE and CWD.
21. The use according to claim 10 or 11,
wherein recombinant production of disulfide mutants of prion proteins or
variants thereof is carried out as "conversion-resistant PrP^C standard" for
25 TSE-tests applied to human or animals, where recombinant PrP^C is amplified
by PrP^{Sc} from pathogenic tissue or bodily fluid such as blood and urine.

22. The use according to claim 10 or 11,

wherein *in vivo* generation of disulfide mutants of prion proteins or variants thereof is carried out in order to enable breeding of TSE-resistant animals by somatic gene therapy with lentiviral vector, where animals include cattle, sheep, cat, elk, deer, pig, horse, and fish.

23. Medicament for the treatment of:

a) neurodegenerative diseases of the group comprising Transmissible Spongiform Encephalopathy (TSE), Alzheimers disease, Multiple Sclerosis, and Parkinsons disease; and/or other

b) conformational diseases of the group comprising Primary systemic amyloidosis, Type II diabetes, and Atrial amyloidosis;

in humans, the medicament comprising a mutant protein or a variant of which comprising at least one additional engineered disulfide bond which inhibits a conformational transition of such proteins.

24. Medicament for the treatment of bovine spongiform encephalopathy (BSE), scrapie in sheep, feline spongiform encephalopathy (FSE), and chronic wasting disease (CWD) in elk and deer, the medicament comprising a mutant protein or a variant of which comprising at least one additional engineered disulfide bond which inhibits a conformational transition of such proteins.